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ENCLOSURES *(Check all that apply)*

- ☐ Fee Transmittal Form
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- ☐ Proprietary Information
- ☐ Status Letter
- ☑ Other Enclosure(s) (please Identify below):

Reference papers:
1. FEMS Microbiol. Lett. 49: 417-422, 1988
2. J. Bacteriol. 154: 1513-1515, 1983

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name			
Signature	Chuan Li		
Printed name	Chuan Li		
Date	June 7, 2005	Reg. No.	

CERTIFICATE OF TRANSMISSION/MAILING

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Signature	Chuan Li		
Typed or printed name	Chuan Li	Date	June 7, 2005

Amendments to a continuation of application: DE NOVO SYNTHESIZED PLASMID, METHODS OF MAKING AND USE THEREOF

Applicant Name: Chuan Li

Date: June 7, 2005

Application/Control Number: 10/068,664

Art Unit: 1636

a.) Introductory Comments

1. In part (c) of claim 6 (withdrawn-currently amended), the phrase "referring entire structure of an existing plasmid" is changed to "using a whole existing plasmid as a structure template" to make the claim clear and to maintain consistence between this claim and new claims.

   In part (a) of claim 16, the term "only" is deleted to make the claim clear.

   In part (a) of claim 16, the phrase "of known functions" is changed to "generated from existing plasmids" to make the claim specific.

   In part (b) of claim 16, the phrase "only with sequences of desirable functions" is changed to "without using a linearized existing plasmid as starting material" to make the claim specific.

   In part (d) of claim 16, the phrase "referring the entire structure of an existing plasmid" is changed to "using a whole existing plasmid as a structure template" to make the claim clear.

2. The present invention is not anticipated by Lereclus and Whitt et al (newly cited US-5,928,897 A and US-6,497,873 B1) for those skilled in the art at time the invention was made.

   The present invention synthesized a plasmid with plasmid elements without using any whole existing plasmid or linearized existing plasmid as starting material. Sequences of unknown or undesirable functions are eliminated during plasmid element preparation. The entire sequences and structure of an existing plasmid is not used in the synthesis of the novel plasmid.

Lereclus teaches, at paragraph bridging columns 22 and 23, plasmid pHT1035 carrying pHT1030 replicon, cat^R gene, and pBR322 origin of replication. However, it is not clear how plasmid pHT1035 was made in the cited patent. The construction of plasmid pHT1035 was described by Lereclus et al and Ferrari et al in FEMS Microbiol. Lett. 49: 417-422, 1988 and J. Bacteriol. 154: 1513-1515, 1983 (copies of these publications are enclosed with this amendment). Lereclus et al described in Table 1 (FEMS Microbiol. Lett. 49: 417-422, 1988) that pHT1035 was constructed by cloning the 2.8 kb BalI fragment containing the replication region of pHT1030 in pJH101 between the HincII and BalI sites. Here one of the starting materials is HincII and BalI linearized plasmid pJH101. Similarly Ferrari et al describes in paragraph bridging column 1 and column 2 (J. Bacteriol. 154: 1513-1515, 1983) that pJH101 was constructed by cloning the 1 kb cat^R gene from plasmid pC194 into PvuII linearized pBR322. Again one of the starting materials is PvuII linearized plasmid pBR322. Both plasmids pHT1035 and pJH101 are made by Boyer and Cohn's teaching (US patent number 4,237,224). This conventional method uses a linearized existing plasmid as starting material. The plasmids made by this method are modifications of the existing plasmid. Lereclus fails to teach that a plasmid can be made directly from pieces of DNA fragments containing replication origin and selection marker without using a linearized existing plasmid as starting material. With teaching of present invention, more complicated plasmids have been made directly from pieces of DNA fragments in a single step without using a whole or a linearized plasmid as starting material. The fact that Lereclus et al used the laborious method to make pHT1035 indicates the disclosed invention is not anticipated by Lereclus et al.

Whitt et al teaches at forth paragraph of column 10 that a Rhabdovirus must have the minimal replicon elements and the N, P, and L proteins and it must contain the M gene. Whitt et al also teaches at last paragraph of column 9 that "these recombinant viruses can be produced (1) entirely use cDNAs or ..." The creation of a modified Rhabdovirus is described in Example 1 of the patent (US-6,497,873 B1). All these cDNAs used by Whitt et al are actually in various plasmids. In the first paragraph of column 17, Whitt et al teaches construction of plasmid pVSV-ΔG used in the virus production. At the third paragraph of column 17, Whitt et al teaches use of pVSV-G

mutant plasmid and plasmids containing the wild-type G, N, P and L genes to produce recombinant virus VSV (Vesicular Stomatitis Virus). Clearly Whitt et al created modified Rhabdovirus using existing plasmids as starting materials. Whitt et al did not anticipate the present invention. In addition, Whitt et al uses different principle of operation than that of the present invention to create virus. The cDNAs used by Whitt et al are first transcribed into RNA and then translated proteins to facilitate the creation of recombinant virus. On the other hand, the DNA fragments disclosed in the present invention are directly assembled by cell to form a plasmid. Using different principle of operation indicates the present invention is not anticipated by Whitt et al.

3. Both Lereclus and Whitt et al use linearized or whole existing plasmids as starting materials to create respective plasmid and virus. The method to make these plasmids is taught by Boyer and Cohn (US-4,237,224). This method has been available for more than 30 years since its publication and it is still used by most scientists today. Because of obvious advantage of saving cellular energy by eliminating sequences of unknown and undesirable functions with the disclosed plasmid and saving time and labor with creating the disclosed plasmid, those skilled in the art surely would have implemented it by now. The fact of lack of implementation for more than 30 years indicates the claimed plasmid is not anticipated by Lereclus and Whitt et al.

4. The disclosed application utilizes a new principle of operation to make the synthesized plasmid. Most plasmids from prior art are synthesized from linearized or whole existing plasmids as starting material. A few plasmids are synthesized by using whole existing plasmid as structure template. Plasmids synthesized from prior arts either using an existing plasmid as starting material or using the entire structure of an existing plasmid as structure template. On the other hand, the disclosed application combines elements of plasmid, neither using a whole existing plasmid as starting material nor referring entire structure of any existing plasmid, to synthesize a new plasmid. With teaching of the application, people can make a plasmid (or any other DNA constructs) from plasmid elements without using an existing plasmid as starting material or referring entire structure of an existing plasmid. The application disclosed a new principle of making a novel plasmid. Therefore the application has blazed a

trail, rather than followed one. Using new principle of operation indicates the disclosed invention is not anticipated by Lereclus and Whitt et al.

5. The disclosed plasmids have unexpected properties. For example, the replication origin of p4T is generated from low copy number plasmid pACYC177; its predicted copy number should be lower than plasmids synthesized from pBR322 and significant lower than the plasmids synthesized from pUC19 according to the teaching from prior arts. However the observed copy number of p4T is higher than or comparable with the plasmids synthesized from pUC19 origin (p3A, Fig. 2) and significant higher than those synthesized from pBR322 origin (p1A, Fig. 2). This unexpected result is contradictory to relevant teachings in molecular biology (Sambrook et al, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y., Vol. 1, page 1.3-1.5 and Table 1.1 page 1.4, 1992) that plasmids with replication origin from pACYC177 are low copy number plasmids. As matter of fact, the disclosed plasmids, that are synthesized from the same replication origin, demonstrate different copy number per cell from low copy number (p2K, Fig.2), intermediate copy number (p4K, Fig. 2), to high copy number (p4T, Fig. 2). These results strongly suggest that the copy number of a plasmid is determined not only by its replication origin but also by its selection marker and the relative structure of the plasmid elements. The different copy numbers of the plasmids generated from pACYC177 replication origin are critical to some of the biomedical applications. The unexpected result of the disclosed plasmid indicates the disclosed invention is not anticipated Lereclus and Whitt et al or by any other prior arts.

In conclusion, the disclosed invention uses novel processes to make plasmids. The novel processes involve a new principle of operation. The de novo synthesized plasmid has novel sequences and novel, sometimes unexpected properties. Some of the properties are contrary to the teachings of prior arts. It is useful in various biomedical applications. It is neither anticipated nor obvious over Lereclus and Whitt et al's teaching or any other prior arts or combination of them. Therefore the re-written claims are submitted that patentable subject matter is clearly present. If the examiner agrees but does not feel that

the present claims are technically adequate, applicant respectfully requests that the examiner write acceptable claims pursuant to MPEP 707.07(j).